SYNTHESIS AND PHARMACOLOGICAL EVALUATION OF NEWLY DERIVED HETEROCYCLIC COMPOUNDS TARGETED FOR NEUROLOGICAL DISORDERS

A

SYNOPSIS

SUBMITTED TO THE

SWAMI RAMANAND TEERTH MARATHWADA UNIVERSITY, NANDED

FOR THE DEGREE

OF

DOCTOR OF PHILOSOPHY

IN

SUBJECT: **PHARMACEUTICAL SCIENCES**

UNDER

THE FACULTY OF SCIENCE & TECHNOLOGY

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2017

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INTRODUCTION:-

There are no therapeutic areas that are more pressing and frustrating than the neurodegenerative diseases. This is not just a common feeling of those like us tirelessly working in the field, but what clearly emerges from an analysis of more than two decades of intense academic and industrial research. Melatonin, the main secretory product of the pineal gland, has been shown to be potentially effective in prevention of numerous types of neurodegenerative disorders in which free radical processes are involved. In brief, melatonin has been found to protect the CNS from beta-amyloid toxicity, glutamate-induced excitotoxicity, nitric oxide toxicity, cyanide toxicity and ischemia/reperfusion injury. It is well known that indole derivatives, extensively present in natural compounds and are very important substances in medicinal and biological aspects. The antioxidant effect of indole ring carrier melatonin has been well described. The development of synthetic compounds capable of mimicking the effects of melatonin has progressed considerably during the past decade. These compounds are structurally diverse and ranged from simple indole derivatives and its bioisosteres to phenylalkylamides and constrained melatoninergic agents. For instances, many heterocyclic moieties have been demonstrated as neuro-protective agents.

Reactive oxygen species (ROS) and reactive nitrogen species (RNS) have gained a lot of importance because of their active role in many diseases. The damage to animal or plant cells and tissues caused by ROS is called oxidative stress. It is caused by an imbalance between the production of ROS and a biological system's ability to detoxify the reactive intermediates or repair the resulting damage. A particularly negative side of oxidative stress is the production of ROS, which include free radicals. Human bodies are constantly exposed to ROS generated from endogenous and some exogenous sources. Antioxidants, both enzymatic and non-enzymatic, prevent oxidative damage to biological molecules by various mechanisms. Melatonin (MLT),

N-acetyl-5-methoxytryptamine is the main secretory product of the pineal gland. Studies have established the role of MLT in many physiological processes, such as the regulation of circadian rhythm and immune functions. Also different therapeutic functions have been proposed for MLT and its derivatives. It is a highly conserved molecule that it acts as a free radical scavenger and a broad-spectrum antioxidant. The ability of MLT to react with free radicals was first shown in 1993, when Tan et al identified its interaction with hydroxyl radicals. MLT has some side effects, but much less so that pharmaceutical sleeping pills. Long-term safety is not known. People with the symptoms of severe mental illness, severe allergies, auto-immune diseases or immune system cancers such as leukemia should not be taking MLT. Despite its possible contribution in the regulation of many physiological processes, two main problems limit its therapeutic use at present. The first is very short biological half-life, due to its fast metabolism to 6-hydroxymelatonin and N (1)-acetyl-N (2)-formyl-5-methoxykynuramine (AFMK) and the second is the lack of selectivity of MLT at target sites. Melatonin, at least in pharmacological concentrations, has the capability of increasing either mRNA levels or the activities of this major antioxidative enzymes[1].

It is well known that indole derivatives, extensively present in natural compounds and are very important substances in medicinal and biological aspects. Indole is a highly conserved molecule that it acts as a free radical scavenger and has broad-spectrum antioxidant activity. Moreover, indole and its derivatives exhibit various therapeutic effects, such as regulation of circadian rhythm and immune functions. Recent research has proved that the indole ring in the melatonin molecule is the reactive center dealing with oxidants due to its high resonance stability and very low activation energy barrier towards free radical reactions. Indole-3-propionamide derivatives exert higher antioxidant activity compared to melatonin. Also, 2-phenylindole

derivatives significantly inhibited lipid peroxidation. L-Tryptophan (TRP) is the precursor amino acid for the synthesis of serotonin (5-HT) and it has been found that 5-HT increases significantly by TRP treatment. Indole ring in the TRP compound acts as ligand of peripheral benzodiazepine receptor (PBR) which improved functional recovery of the brain in neuro-intoxicated animal models due to its neuroprotective effect. In addition, TRP is the precursor of melatonin which could save both dopaminergic and non-dopaminergic neurons from oxidative stress and protect all types of brain damaged neurons. A large variety of synthetic compounds have been identified as potent neuroprotective agents[2].

NEED OF STUDY:-

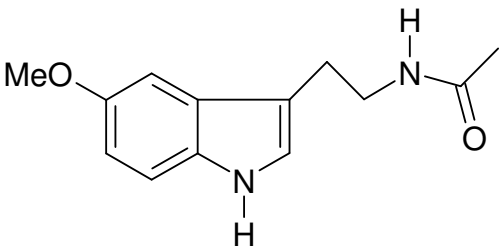
Neurodegeneration is the progressive loss of structure or function of neurons because of tireless working of peoples and aging /oxidative stress so neuron partially or completely loss its activity and produce chronic diseases such as Alzheimer, Parkinson, Schizophrenia and other diseases.

Melatonin & serotonin has been involved in variety of physiological actions such as antioxidant, effective in prevention of numerous types of neurodegenerative disorders in which free radical processes are involved. In brief, melatonin has been found to protect the CNS from beta-amyloid toxicity, glutamate-induced excitotoxicity, nitric oxide toxicity, cyanide toxicity and ischemia/reperfusion injury.

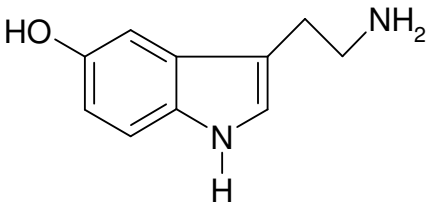
The effect of melatonin to neutralize the free radicals is receptor independent. Based on the investigation of structure-activity relationships of the melatonin molecule it has disclosed that the reactive center of dealings with oxidants due to its high resonance stability and very low activation energy barrier towards the free radical reactions. In recent years, many physiological

properties of MLT have been described resulting in much attention in the development of synthetic compounds possessing melatonergic activity. However, the therapy of oxidative stress-related diseases has not found satisfactory application in clinical practice. This may be due to the insufficient efficacy of drugs available, their unsuitable pharmacokinetic side effects and toxicity[3].

The present investigation is mainly focused on the synthesis and QSAR study of new melatonergic and serotonergic synthetic agents for better neurological activity, less side effect and greener synthetic mode.



(i)



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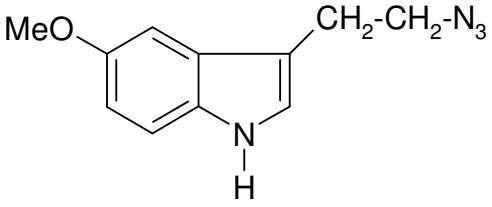
REVIEW OF LITERATURE:-

A significant amount of data collected in a literature survey which high lighten the various methods for synthesis of substituted indole by several investigator. The survey also shown indole heterocyclic compound is able to reveal a good neuroprotective & anti-oxidant activity.

Natalia A. Lozinskaya[4]*et al*, Synthesized spiroindole as a melatonin agonist agent from 2-(-indolin-3-ylidene) acetonitrile by cycloaddition reaction the synthesized compound shows promising biological action.

Andrew T[5]*et al,* have design, Synthesis a new azidoisothiocyanto substituted indole as a Melatonergic agonist agent. In this process 5-methoxy substitute of azido (iii) & isothiocyanto (iv) shows most potent biological action than other substitute.



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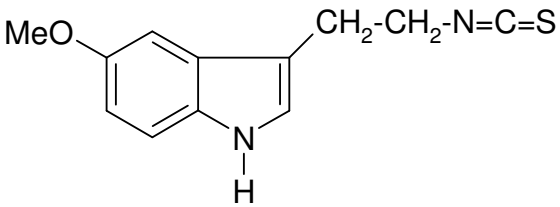
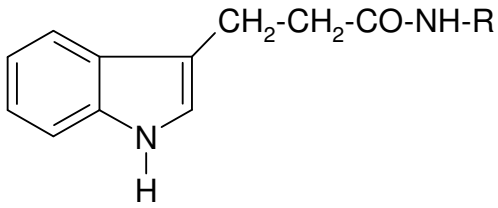


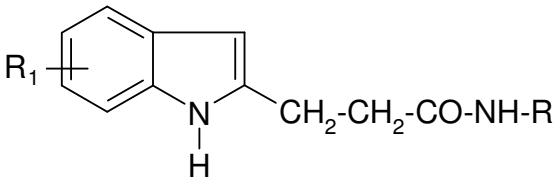
(iv)

Zeynepates A[6]*et al*, have carried out a comparative study and evaluation of Melatonin and Indole 3-propronic acid derivatives (v) which shows good biological activity.



(v)

Gilberto S[7]*et al*, have synthesize and structure active relationship for a novel 2-(N-acylaminoethyl) indole (vi) with melatonin –like cytoprotective activity.



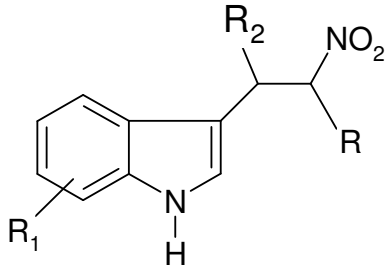
(vi)

Tatsuki K[8]*et al*, have synthesized 1,6-Dihydro-2H-indeno[5,4-b]furan derivatives and carried out pharmacological screening for MT_2-selective agonist agent.

Mario FR [9]*et al*, have synthesis of N-acetyl derivatives of melatonin and carried out physicochemical properties and Pharmacological activity.

SibelSüzen*t*[10] *al*, have synthesis a synthetic indole derivatives and carried out antioxidant activity. Synthesis of indole derivative compounds is under investigation to determine which exhibit the highest activity with the lowest side effects. Epidemiological studies have been strongly suggesting that antioxidants can decrease the rate of many diseases.

Stefano Lancianesi[11]*et al*, have synthesis of series of substituted 3-(2-nitroalkyl) indole (vii) and carried out neuroprotective activity which shows potent biological activity.



(vii)

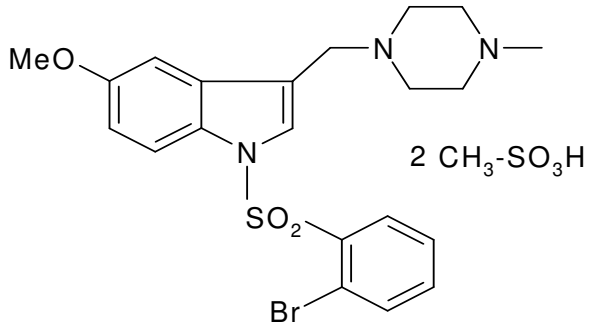
AlessiaC[12]*et al*, have been synthesized several substituted Indole derivatives in which these compound screened for melatonin agonist agent.

Giorgio T[13]*et al*, new series of indole melatonin analogues, bearing the amido ethyl side chain attached at the N-1 position of the indole nucleus, were synthesized and tested for their affinity for the melatonin receptor.

E. Duranti[14]*et al,* synthesized the bromination of melatonin agent in which they found2-Bromomelatonin behaved as a potent agonist in the physiological studies. It showed enhanced activity in inhibiting the spontaneous firing activity of cortical neurons and similarly to melatonin and 2-iodomelatonin potentiated significantly the inhibitory effect of GABA.

Marco M[15]*et al*, have synthesis of new melatonin derivatives and comprehensive Comparative Molecular Field Analysis (CoMFA) Study.

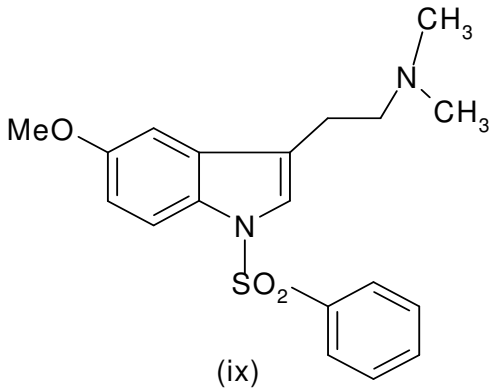
Ramakrishna N[16]*et al*, have synthesize a novel 1-[(2-Bromophenyl)sulfonyl]-5-methoxy-3-[(4-methyl-1-piperazinyl)methyl]-1H-indole Dimesylate (viii) and carried out pharmacological activity and shows a potent action against Alzheimer disease.



(viii)

Derek CC[17] et al, have synthesis of series of indole derivatives and carried biological activity as serotonin receptor agonist agent.

Michael GNR[18] et al, have synthesis of N-aryl sulphonyl indole and evaluate for pharmacological screening. A series of N_1-arylsulfonyltryptamines were found to be potent ligands of the human serotonin 5-HT6 receptor with the 5-methoxy-1-benzenesulfonyl analogue (**ix**) having the highest affinity.



(ix)

Gilberto S[19]*et al*, explain the circadian nature of melatonin (MLT) secretion, coupled with the localization of MLT receptors to the suprachiasmatic nucleus, has led to numerous studies of the role of MLT in modulation of the sleep-wake cycle and circadian rhythms in humans.

Marco M[20]*et al*, have synthesized various new substituted Indole derivatives as melatonin agonist agent and screened this derivatives for antioxidant and cyto protective activities. Few of the derivatives show promising antioxidant activity.

OBJECTIVES OF STUDY:-

The present work is undertaken with the following objectives:

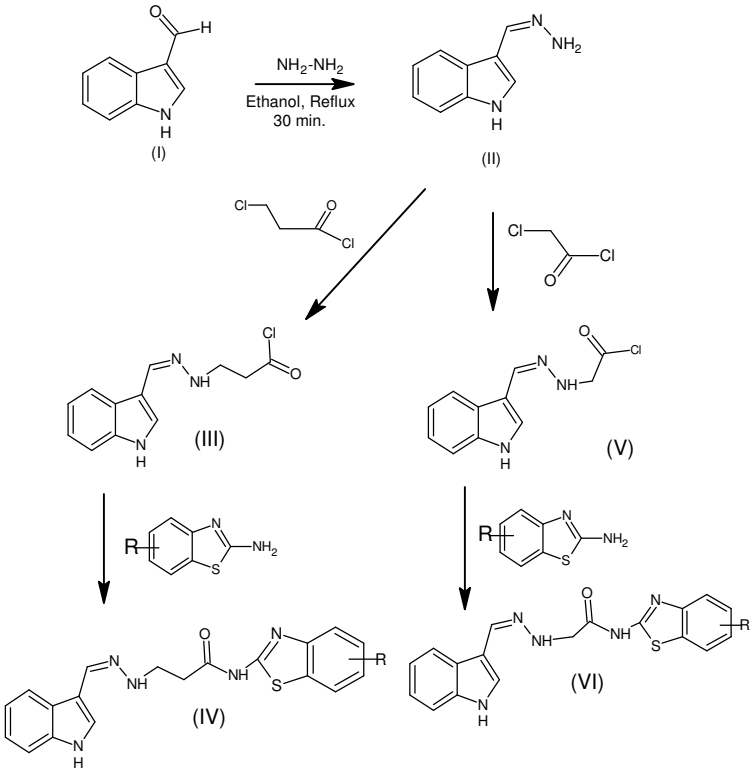
1. To synthesize novel molecules targeted for neuroprotection which mimic the property of magic hormones.
2. To establish the structure of synthesized novel compound based on chemical and spectral data.
3. To carry out QSAR studies in order to optimize the structure for further development.
4. To carry out the Pharmacological screening (Neuroprotective, antioxidant & antidepressant) of synthesized compound.

MATERIALS & METHODS:-

Proposed Synthetic Pathway:-I

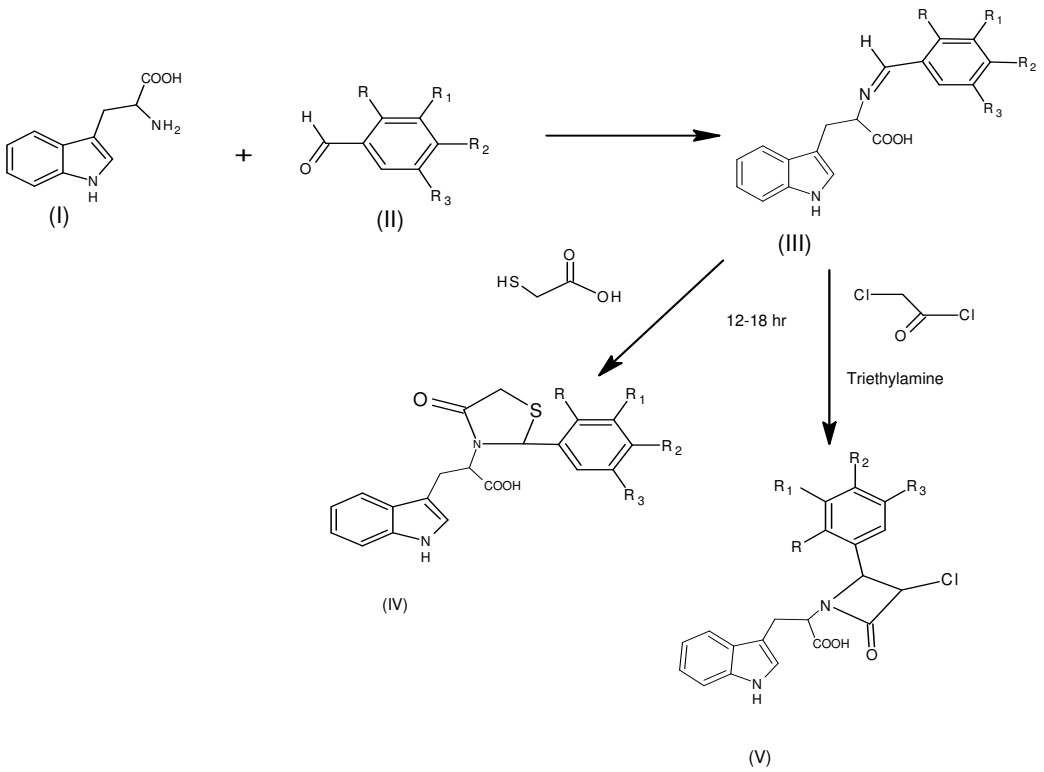
A Substituted indole 3-aldehyde (I) refluxed with hydrazine to yield a product of hydrazide substituted indole (II), then hydrazide substituted indole is heated with chloro ethyl acetyl chloride as result gives Indole intermediate compound (III), then it is further reacted with substituted 2-amino benzothiazole gives novel heterocyclic compound (IV) . A hydrazide substituted indole (II) refluxed with chloro acetyl chloride then formation of intermediate

compound (V), which is later reacted with substituted 2- amino benzothiazole, gives series of new heterocyclic compound (VI).



Proposed Synthetic Pathway:-II

A substituted amine (I) refluxed with substituted benzaldehyde (II) then formation of substituted indole intermediate compound (III). When substituted indole intermediate compound is reacted with thioglycolic acid gives Indole substituted 1, 3-thiazol-4-one (IV), substituted indole intermediate compound refluxed with chloro acetyl chloride then formation a product of azetidinones (V).



Characterization of synthesized compounds:

By Chromatographic & Spectroscopic Techniques

Chemicals and other reagents will be collected from standard companies. The compounds will be synthesized. The product will purified by chromatographic technique column chromatography, preparative chromatography.

The chemical structure of the synthesized compounds is established on the basis of Physical, chemical and analytical data, melting point of synthesized compound is determined in one capillary tube and is uncorrected. They expressed in degree centigrade.

The selected synthesized compounds will be characterized by UV, IR, NMR and Mass spectral data. This will be collected by sending the sample to other advanced research centre like NCL, Pune.

The main objective of the present investigation is to explore newer heterocyclic molecule with potent neuroprotective action.

QSAR Investigation:-

1. To carry out QSAR studies for optimizing structure active relationship of functional groups present in a leading structure in terms of their biological endpoint[21.]
2. Quantitative structure activity relationship (QSAR) is an attempt to correlate structure descriptor of molecule with their physicochemical properties and biological activities.
3. Docking is a tool used in computational drug design predicting whether a particular compound will be a good inhibitor of particular protein[22].
4. QSAR studies use to reduce the time and money for drug design.
5. QSAR currently are being applied in many discipline, with many pertaining to drug design the main step implicated in this method include data collection, molecular description selection and procurement, correlation model development and finally model evolution.
6. To understand the relationship between structure and biological activity, for synthesized ring substituted derivatives a QSAR analysis will be carried out by generation of any possible QSAR model [23].
7. The QSAR investigation will be carried out by VLIFE, Schrödinger and other suitable software.

Pharmacological Investigation:-

Today the neurological diseases major concerns in world, near about 10-15% of the people are suffering due to neurological disorder. Large amount of drug shows significant side effect. So our aim studies to screen the synthesized compound for neurological diseases (such as Neurological pain[24]/Alzheimer/stroke[25]) by using a suitable Pharmacological Model. It is way to explore the synthesized compound for good Pharmacological activities.

Source of Data

The data of present literature and for further investigation will be carried out by referring different Heterocyclic book, chemical abstract, National & International journal on Synthetic procedure, on Medicinal approach and by depending on Pharmacological activity.

The data will be carried out by referring following National & International Journals

Journals:-Journal of Medicinal Chemistry, European journal of medicinal chemistry, Bioorganic and medicinal chemistry Letters, Pharmaceutical chemistry journal, Behavior, Thieme, Tetrahedron letters, Pharmacology, Biochemistry, Biomedicine, Pharmacotherapy, Indian journal of Pharmacology, Indian journal of physiology and pharmacology, European journal of Pharmacology.

The data will be collected from, Library facility in our college by referring e-journals, National Chemical laboratory and Indian Institute of science.

Scheme for proposed research work:-

Sr. No	RESEARCH WORK	TENTATIVE TIME IN MONTH
1	Literature Survey	03
2	Design of New compound & synthesis Planning	02
3	Procurement of drug, Chemicals and setting up the method for synthesis of title compound.	01
4	Synthesis of newer compound through VLIFE, Schrodinger QSAR suggestion	16
5	Purification and characterization of the new synthesized compounds A. Melting point determination B. Determination of IR, Mass and NMR spectra. C. Elemental analysis	03
6	QSAR investigation	03
7	Pharmacological evaluation of synthesized drug	05
8	Completion of research work and thesis writing	03

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